Carrier detection and phenotypic expression in a family with hereditary coproporphyria

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Statutory Declaration

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Naz AL Hafid

Date

16/7/08

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List of Abbreviations

AIP	Acute Intermittent Porphyria
ALA	δ-Aminoluvilinic Acid
ALAS	δ-Aminoluvilinic Acid Synthase
APS	Ammonium Persulfate
CPOX	Coproporphyrinogen Oxidase
DHPLC	Denaturing High Performance Liquid Chromatography
ESE	Exonic Splicing Enhancers
HCP	Hereditary Coproporphyria
HMBS	Hydroxymethylbilane synthase
PAGE	Polyacrylamide Gel Electrophoresis
PBG	Porphobilinogen
PBGD	Porphobilinogen Deaminase
PCT	Porphyria Cutania Tarda
PPOX	Protoporphyrin Oxidase
SSCP	Single Stranded Conformation Polymorphism
UROD	Uroporphobilinogen Deaminase
VP	Variegate Porphyria
WFI	Water For Injection

Publications Arising From This Thesis

Poster Abstracts

AL Hafid N, Poulos V, Bennetts B, Simpson A, Carpenter K, Stewart P (2007) Mutation screening and carrier detection in a family with hereditary coproporphyria (HCP). European Porphyria Initiative, Rotterdam, The Netherlands.

AL Hafid N, Poulos V, Bennetts B, Simpson A, Stewart P (2006) Identification of a novel mutation in a family with hereditary coproporphyria (HCP). 10th International Congress of Inborn Errors of Metabolism, Chiba, Japan.

Naz AL HAFID, Victor POULOS, Bruce BENNETTS, Ann M. SIMPSON, Kevin CARPENTER, Peter STEWART (2006) Mutation screening in the coproporphyrinogen oxidase gene in patients with HCP: Identification of a novel mutation. AIMS AACB Scientific Conference, Hobart, Australia. - **Won first prize for best poster.**

Oral Presentations

Western Sydney Genetics Program (2005) – The children's Hospital at Westmead. The Study of Penetrance And Carrier Detection In Acute Intermittent Porphyria.

European Porphyria Initiative conference (2007) – Rotterdam, The Netherlands. Mutation screening and carrier detection in a family with hereditary coproporphyria (HCP). European Porphyria Initiative, Rotterdam, The Netherlands.

ABSTRACT

Carrier Detection and phenotypic expression in a family with hereditary coproporphyria

Introduction: Hereditary coproporphyria (HCP) is an autosomal dominant disorder that results from defects in the enzyme coproporphyrinogen oxidase (CPOX). A major clinical feature is neurologic damage that leads to peripheral and autonomic neuropathies and psychiatric manifestations, accompanied occasionally by cutaneous skin lesions. HCP symptoms are usually triggered by environmental factors such as drugs and hormones. However, the penetrance is low meaning that most patients remain asymptomatic most of their lives. This makes it more difficult to diagnose asymptomatic HCP patients by solely relying on biochemical methods. The aim of this study was to genetically screen carriers in a family with HCP and design a questionnaire to identify subtle porphyria symptoms.

Methods: Mutation screening was carried out in a family of thirty members, two of whom were symptomatic for HCP. The entire *CPOX* gene of the proband was screened for mutations. A questionnaire was designed and completed by 26 participants to review the clinical picture and life style of patients and was compared with the genetic data.

Results: A novel mutation was identified in exon 5 at c.1064A>C causing a substitution in amino acid 355 from glutamine to proline (p.Q355P). Sequencing results revealed that sixteen out of thirty members of this family were carriers of the mutation. Porphyria related symptoms were noted to be as common in males as in females with the mutation.

Conclusions: Patients with the Q355P mutation reported more symptoms than those without the mutation. Females reportedly are more likely to exhibit acute porphyria symptoms due to hormonal factors. However, it was noted that the number of symptoms reported by males with the mutation was more than that reported by females with the mutation. In this small sample cohort, these results suggest that environmental factors rather than endocrine factors play a role in the phenotypic expression of this mutation. Carriers are at risk of acute attacks; identifying them is beneficial because they can be given prior advice of preventative measures.